REMARKS

I. Status of the claims

Claims 1 and 3 are pending in this application, with claims 4-17 withdrawn from consideration and canceled. Claim 1 has been amended in order to more clearly explain the subject matter of the invention. No claim was amended in order to overcome prior art. Furthermore, the scope of the claims was not narrowed by these amendments. No new matter has been added by these amendments.

II. Rejections under 35 U.S.C. § 112, second paragraph

The Office rejected claims 1 and 3 under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Applicant respectfully traverses this rejection.

In particular, the Office argues that "there is no determining of anything" in claim 1. Office action dated October 11, 2002, (the Office Action) at p. 2, line 13. Applicant respectfully disagrees with the Office's view. However, with the sole purpose of expediting prosecution, Applicant has amended claim 1 in order to better claim the subject matter of the invention. In particular, the claim now explicitly recites the step of "determining whether the test substance inhibits or acts as a ligand of the binding domain of the protein." Accordingly, Applicant respectfully requests that this rejection be withdrawn.

The Office alleges that "[i]n claim 1, it is unclear what the comparing is of, for example, is the test substance present in the control mixture?" and further argues that "[i]t is unclear as to how the controls differ from the tests." Office Action at p. 2, lines 13-16.

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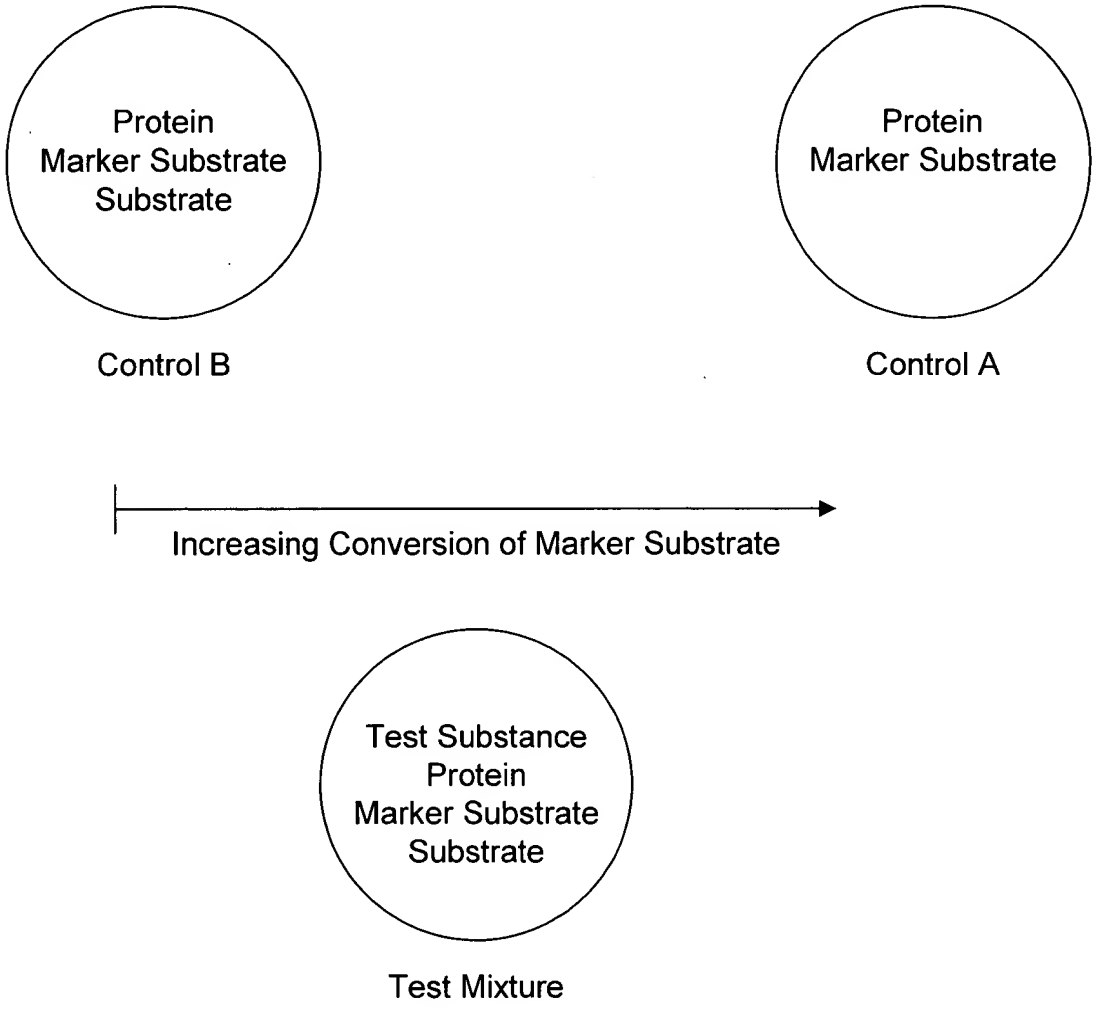
According to claim 1 of the invention, a test substance can be identified as an inhibitor or ligand of the binding domain a protein by comparing the conversion of a marker substrate in the presence of the test substance with the corresponding conversion occurring in appropriate control mixtures, which do not contain the test substance. *See, e.g.*, Table 1 and Examples 1-2.

Applicant uses the following figure to assist in explaining the invention:



One control mixture, named control mixture A in claim 1, comprises the protein and marker substrate. In this control mixture, the conversion of the marker substrate in the presence of the protein is high, relatively speaking, as there is no competition for

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binding of the catalytic domain. The other control mixture, named control mixture B in claim 1, comprises the protein, marker substrate, and substrate. The conversion of the marker substrate in this mixture is lower than that in control mixture A. This is because the substrate competes with the marker substrate for binding to the catalytic domain of the protein.

The present invention states that when the conversion of the marker substrate in the test mixture is of a value between the conversions in control mixtures A and B, then the test substrate inhibits or acts as a ligand of the binding domain of the protein. One skilled in the art is more than capable of understanding the compositions of the control mixtures and test mixture and of doing this comparison. Certainly, none of the mixtures or steps described here should be considered "indefinite."

In light of the above, Applicant submits that the purpose of the control mixtures A and B in claim 1 is clear and the claim not indefinite. Accordingly, Applicant respectfully requests that this rejection be withdrawn.

The Office finally argues that "[t]here is lack of antecedent basis in several instances, for example, the conversion." Applicant respectfully disagrees.

The Office indicates that there is lack of antecedent basis in *several* instances, but mentions *only one* example, which relates to the term "conversion." With respect to that assertion, Applicant points out that conversion of a marker substrate is inherent in a mixture containing an enzyme and such marker substrate. By definition, a "marker substrate is a compound which is...chemically converted by the catalytic domain [of the protein] and allows monitoring of the conversion reaction." Specification at p. 3, lines 4-7. Therefore, it is appropriate for Applicant to refer to "the conversion" of the

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marker substrate. Accordingly, Applicant respectfully requests that this rejection be withdrawn. Applicant believes that all other terms in the claim also have the appropriate antecedent basis where needed. Applicant respectfully requests clarification of the Office's comment regarding lack of antecedent basis "in several instances."

III. Rejections under 35 U.S.C. § 103(a)

The Office rejected claims 1 and 3 under 35 U.S.C. § 103(a) as being unpatentable over *Stack* (Stack, M.S. and R.D., Gray, J. Biol. Chem., 264(3):4277-81 (1989)) and *Khanna* (U.S. patent No. 5,434,052). Applicant respectfully traverses these rejections. Moreover, applicant respectfully requests clarification of the Office's statement on page 2 of the Office Action that "[i]f the limitations of claim 3 were incorporated into claim 1, the claimed material would be allowable." The Office's offer appears inconsistent with the rejection of claim 3 over the cited art.

Stack

The Office argues that *Stack* discloses inhibitors of collagenase on substrates and that in order to determine whether soluble collagen could inhibit hydrolysis of a synthetic substrate by collagenase, hydrolysis was measured in increasing concentrations of collagen. In the Office's opinion, the instant claims differ from the teachings in *Stack* "in that[, as opposed to a single control in *Stack*,] claim 1 recites two controls are employed, one without the substrate and one with the substrate." Office Action at p. 4, lines 1-3. The Office further alleges that "[i]t would have been obvious to one of ordinary skill in the art at the time the invention was made to [use] controls with and without the substrate because both of the above references teach assaying inhibition with substrate and one would know the activity of the enzyme prior to studying

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its inhibition upon a given substrate," and that "[n]o novelty is seen in employing controls in assays." Office Action at p. 4, lines 5-17. Applicant respectfully disagrees.

The Office is respectfully reminded that in order to prove a *prima facie* case of obviousness, the Office needs to establish, *inter alia*, that all instant claim limitations are taught or suggested by the prior art. M.P.E.P. § 2143.03. Unlike instant claim 1, which recites a mixture comprising a marker substrate, *Stack's* solutions do not contain such an element. *Stack* only discloses solutions comprising a protein (collagenase or gelatinase), a substrate (collagen in various experiments and a synthetic peptide in another experiment), and a test substance (a synthetic peptide in one case and Eriochrome Black T in another case), but there is no disclosure in *Stack* of a mixture comprising a protein, a substrate, a maker substrate, and a test substance. In fact, there is no discussion in *Stack* about a marker substrate at all. *Stack* cannot possibly suggest the claimed invention, which relies on a comparison of conversions of that marker substrate to determine whether the test substrate inhibits or acts as a ligand of the binding domain of the protein.

The following discussion identifies the components of certain compositions disclosed in *Stack*. *Stack* reports that when Eriochrome Black T "was *tested* with the synthetic substrate, [Eriochrome Black T] gave 56% inhibition of collagenase." *Stack* at p. 4279, col. 1, 2nd full ¶ (emphasis added). In this experiment, the protein was collagenase, the substrate was the synthetic peptide, and the test substance was Eriochrome Black T. *Stack* also indicates that "[t]he synthetic substrate was therefore used to determine the inhibitory potency of [a mercaptomethyl analogue of leucine] with collagenase and gelatinase." *Stack* at p. 4279, col. 1, 1st full ¶. In this case, the protein

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was either collagenase or gelatinase, the substrate was again the synthetic peptide, and the test substance was a mercaptomethyl analogue of leucine. In a further described experiment, *Stack* discloses that "collagen is a competitive inhibitor of collagenase action on the peptide." *Stack* at p. 4279, col. 1, 3rd full ¶. In this case, the protein was collagenase, the substrate was collagen, and the test substance was the synthetic peptide. It is clear that no marker substrate was used in any of these compositions. Should the office argue that *Stack's* synthetic peptide or Eriochrome Black T are marker substrates, *Stack's* solutions would still be lacking at least one element of the instant claims, either a substrate or a test substance. For at least this reason, *Stack* falls far short of teaching or suggesting all limitations of the invention, including the control mixture B, the text mixture, and the comparison of conversion of the marker substrate. Applicant respectfully requests that this rejection be withdrawn.

Furthermore, nowhere in *Stack* is there a teaching "to find substances which reduce or essentially prevent binding of substrates to the *binding* domain of a protein." Specification at p. 2, lines 5-6 (emphasis added). *Stack's* disclosure only refers to the catalytic site (active site) of the protein and, contrary to the Office's assertion, *Stack* does not discuss binding sites at all. In fact, *Stack* appears mostly concerned with comparing "the kinetic constants for the hydrolysis of synthetic substrates by collagenase and gelatinase [because such comparisons] should provide insight into differences between these two enzymes." *Stack* at p. 4277, col. 2, 2nd full ¶. When comparing the kinetic constants for the *hydrolysis* of synthetic substrates, *Stack* is indicating that the experiments described therein will focus on the inhibition of the *catalytic* site of the enzymes.

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In light of the foregoing remarks, Applicant submits that the invention would not have been obvious in light of *Stack*, and respectfully requests that this rejection be withdrawn.

Khanna

The Office argues that *Khanna* "teaches in claim 8 evaluating binding inhibition of a compound by combining a receptor and a compound, adding a marker, and determining binding." Office Action at p. 3, lines 13-16. Just as in *Stack*, the office alleges that the instant claims differ from the teachings in the reference "in that[, as opposed to a single control in *Khanna*,] claim 1 recites two controls are employed, one without the substrate and one with the substrate." Office Action at p. 4, lines 1-3. Also as with *Stack*, the Office further argues that "[i]t would have been obvious to one of ordinary skill in the art at the time the invention was made to controls with and without the substrate because both of the above references teach assaying inhibition with substrate and one would know the activity of the enzyme prior to studying its inhibition upon a given substrate," and that "[n]o novelty is seen in employing controls in assays." Office Action at p. 4, lines 5-17. Applicant respectfully disagrees.

In this case, the Office has also failed to show a *prima facie* case of obviousness because *Khanna* does not teach or suggest all the limitations of the instant claims. M.P.E.P. § 2143.03.

Like *Stack*, *Khanna* also fails to disclose a marker substrate and, therefore, fails to disclose any control mixture B, the claimed test mixture, and the claimed comparison of conversions of the marker substrate. *Khanna*'s solutions comprise a proteinaceous receptor (which may correspond to the protein in the instant claims), a substrate (a

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conjugate formed by covalently bonding the natural ligand of the receptor to an enzyme donor), and a test compound. *See, e.g.*, *Khanna* at col. 1, lines 49-67; claim 8.

In *Khanna*, an enzyme acceptor is also added to the solution in order to combine with the enzyme donor (a fragment of ß-galactosidase) and generate an active form of ß-galactosidase, which is used as a means to monitor the binding of the test substrate (ligand) to the protein. *See*, *Khanna* at col. 1, lines 61-67; col. 2, lines 26-32; last ¶ in claim 8. That is, because the products of the hydrolysis of the substrate of ß-galactosidase are easily detectable via ultraviolet spectroscopy, the ß-galactosidase system is used as an indirect method to study the type and nature of the interactions between the test compound and the protein (receptor). It should be noted, however, that the holoenzyme ß-galactosidase, the components that together generate ß-galactosidase (the enzyme acceptor and the enzyme donor), and the substrate for ß-galactosidase are not part of the protein/receptor system for which *Khanna* is trying to find ligands. The sole purpose of these ß-galactosidase-related compounds appears to be to provide the means to monitor the binding interactions between the proteinaceous receptor and any potential ligand (test compound). *See, e.g.*, *Khanna* at Abstract and claim 8. Therefore, none of the components of the ß-galactosidase system qualify as a marker substrate because none of them are converted by the protein of interest (proteinaceous receptor). Specification at p. 3, lines 4-7.

Because *Khanna* does not teach a marker substrate, *Khanna* does not teach all of the limitations of the present claims. Just as with *Stack*, this disclosure cannot suggest the claimed invention, because the claimed invention recites a comparison of

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conversion of that marker substrate to determine the properties of the test substance. Applicant respectfully requests that this rejection be withdrawn.

In light of the foregoing remarks, Applicant submits that the invention would not have been obvious in light of *Khanna*, and respectfully requests that this rejection be withdrawn

CONCLUSION

Applicant respectfully requests that this Amendment under 37 C.F.R. § 1.116 be entered by the Office, placing claims 1 and 3 in condition for allowance. Applicant submits that the proposed amendment of claim 1 does not raise new issues or necessitate the undertaking of any additional search of the art by the Examiner, because all of the elements and their relationships claimed were either earlier claimed or inherent in the claims as examined. Therefore, this Amendment should allow for immediate action by the Office.

Furthermore, Applicant respectfully points out that the final Office Action by the Office presented some new arguments as to the application of the art against Applicant's invention. It is respectfully submitted that the entering of the Amendment would allow the Applicant to reply to the final rejections and place the application in condition for allowance.

Finally, applicant submits that the entry of the amendment would place the application in better form for appeal, should the Examiner dispute the patentability of the pending claims.

In view of the foregoing remarks, Applicant submits that this claimed invention, as amended, is neither anticipated nor rendered obvious in view of the prior art

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references cited against this application. Applicant therefore requests the entry of this Amendment, the Office's reconsideration and reexamination of the application, and the timely allowance of the pending claims.

Please grant any extensions of time required to enter this response and charge any additional required fees to our deposit account 06-0916.

Respectfully submitted,

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APPENDIX TO AMENDMENT OF FEBRUARY 6, 2003

Amendments to the claims

1. (Three Times Amended.) A method to determine whether a test substance inhibits or acts as a ligand of a binding domain of a protein, comprising:

incubating said test substance with a mixture,

wherein said mixture comprises:

a) the protein,

b) at least one marker substrate, and

c) at least one substrate; and

determining whether the test substance inhibits or acts as a ligand of the binding domain of the protein by comparing the conversion of the marker substrate in the presence of the test substance with the corresponding conversion in control mixtures A and B,

wherein the control mixture A comprises the protein and the marker substrate; and the control mixture B comprises the protein, the substrate, and the marker substrate, and

wherein the test substance is an inhibitor or ligand of the binding domain of the protein if the conversion of the marker substrate in the presence of the test substance is between the values obtained with control mixtures A and B.

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